CONFIDENTIAL MATERIAL

THE UNIVERSITY OF BIRMINGHAM

BIOMEDICAL ETHICAL REVIEW SUB-COMMITTEE (BERSC)

13th November 2014

MINUTES

14/11-02 Minutes

The minutes of the meeting held on 25th September 2014 were considered by the Committee and were approved subject to minor amendments.

14/11-03 Matters Arising

Minute 14/09-07-4 "Study & treatment in model of liver transplant"

This application has now been granted approval by the Home Office.

Minute 14/09-07-1 "Innate lymphoid cell functions in vivo"

This application has now been granted approval by the Home Office.

Minute 14/09-07-3 "Validation of anti-angiogenic and vascular targets in cancer"

This application is awaiting comments from the Home Office Inspector.

Minute 14/09-07-2 "Arginine methylation and tumourigenesis

This application is currently receiving final comments, and it is hoped that Home Office approval will be possible by the end of the year.

14/11-04 Chairperson's Items

No Chairperson's items were reported.

14/11-05 Verbal Reports from the Director of BMSU and Named

Persons

Report from Director of BMSU:

The Director of BMSU reported that the Unit is running smoothly.

New post-mortem tables have been installed and are to be commissioned shortly.

By the end of 2014, BERSC will have processed 17 project licences, indicating the extent of the animal work being carried out at Birmingham. It is anticipated that fewer licences will be submitted during 2015, as many projects will already be underway.

It was noted that one particular licence due for renewal in 2015 is extremely large, and it is likely that it will have to be broken down into several separate applications. It will not be possible to get all of these ethics applications renewed prior to the expiry of the existing licence, and so one of the more simple elements of the project will be reviewed early in the year to hopefully avoid a hiatus.

The costs associated with personal licences have increased, and licence holders are being asked to inform BMSU if a personal licence is no longer required.

In relation to the import/export of animals, health screening is ongoing within BMSU.

An application has been made for funding to allow four people to attend the forthcoming LASA conference.

It is hoped that the Chair of BERSC will be able to attend the forthcoming RSPCA Lay Forum, and will feedback on the event to the Committee.

An internal forum has taken place for users of BMSU, and this was attended by the Home Office Inspectors. Helpful, two-way feedback was provided.

Report from Named Veterinary Surgeon:

The Named Veterinary Surgeon reported that there is still some presence of mouse norovirus and pasteurella within BMSU, but appropriate action is being taken and it should have no impact upon either the welfare of the animals or the validity of the experiments carried out within the Unit.

14/11-06 Report from the Fast Track Procedure (including SharePoint drive)

It was reported that the fast track procedure is up-to-date, and that there are no outstanding issues.

A SharePoint site has been set up as a repository for BERSC-related documents, and it will hopefully also allow members of BERSC to discuss issues online. Papers to be considered via the fast track system will be loaded onto SharePoint.

A presentation was given on the features of SharePoint 2013.

As discussions at BERSC are minuted, the online discussion function will not be suitable for the discussion of applications requiring full review. It was suggested that SharePoint could prove very useful in allowing Committee members to see subsequent and final versions of applications, after consideration at BERSC has taken place.

14/11-07 Project Licence Proposals

14/11-07-1 Application Ref TBA – Regulation and mechanism of platelet activation by GPVI and CLEC-2

The aim of this project is to determine how platelet function is regulated by CLEC-2 and/or GPVI activation, and how those receptors are assembled into macromolecular complexes in order to carry out that role.

The PI gave a presentation explaining the application to the Committee. It was explained that the licence currently covering this work is shortly due to expire. The existing licence has been very well managed, and has run smoothly over the past five years. The only new elements in the new licence application are the reverse passive Arthus reaction and some discussion of the refinements from which the work will benefit. It was noted that the wound healing model is relatively new, but is already being used within BMSU as a part of other licences.

One significant refinement which has been made in this application is that the proposed tail bleeding assay will be carried out under terminal anaesthesia, whereas in the existing licence, tail bleeding is carried out under recovery anaesthesia. This change will minimise any animal welfare implications, and will also increase the amount of useful data which can be obtained from the animals.

The explanation of the blood collection protocols should be moved into section E of the application.

With reference to the reverse passive Arthus reaction, it must be made clear in the application that the animals will be humanely killed after

four hours. The Arthus reaction is considered the 'gold standard' model, although there are less refined, alternative models which involve the eye vasculature. The researchers are not aware of this model being used elsewhere in the UK, but a member of the research group does have experience with the required techniques. It was suggested that the researcher with relevant experience should review the 'adverse effects' section of the application and make any necessary additions.

25,000 mice will be bred, but only 3,000 will be used for experiments. Whilst these breeding numbers are high, the licence will span five years and these numbers are upper limits, so it is likely that fewer animals will be required in reality. As all animals will have at least one genetic mutation, and some more than one, high breeding numbers are required. The intended use of microscopy, and the associated need to insert coloured proteins, also increases the breeding numbers.

It was explained that the statistics used in this work should be straightforward, and there is expert statistical advice available within the University if required. This should be stated within the application.

Given the nature of the experiments, opiate rather than NSAID analgesia will be used.

While there are welfare costs associated with the use of radiation chimeras, BMSU has considerable experience with and understanding of these effects. There are also welfare issues associated with the use of tamoxifen, and the Committee considered the 'pay off' between the numbers of radiation chimeras used and the administration of tamoxifen.

The lay summary should be revisited to ensure that where possible, any technical wording is replaced or explained – for example, the replacement of 'vasculature' with 'blood vessels'.

In relation to adverse effects, it should be clarified that either infection or any of the other listed symptoms/indications is sufficient to necessitate killing via a Schedule 1 method. It should also be made very clear that if an animal is in pain it will be given analgesia, and if the pain cannot be rapidly alleviated the animal will be humanely killed. It was explained that BMSU uses an in-house 'pain grimace scale' to assess whether an animal is experiencing pain. The approach followed in relation to pain scoring should be explained in the lay summary.

Within the application, where necessary the species should stated as 'mouse'.

There was some discussion about the actual differences between protocols 1 and 2, and how these differences should be explained in the

application. It was clarified that the main actual difference is that the phenotypes which may arise place protocol 2 in the 'moderate' severity bracket, although the protocols also differ in respect to the tamoxifen treatment and the proposed induction.

Weight loss may be associated with the tamoxifen treatment, and it was queried whether any particular action would be taken in an effort to maintain the animals' weight. It was explained that weight loss exceeding 10% is seen in approximately 20% animals, but that these animals do usually rally. In similar studies, the diet has been manipulated to minimise weight loss; the researchers will try this.

Protocol 4 is classified as 'moderate' severity because of the proposed manipulation of diet, and the use of radiation chimeras.

Depth of anaesthesia will be assessed via pedal reflex. The PI explained that very few animals die under intravital anaesthesia.

Resolved that:

With revisions as discussed above, the Chair will recommend that the Establishment Licence Holder submits the application to the Home Office.

14/11-07-2 <u>Application Ref TBA – The pathophysiological roles of podoplanin and its receptor CLEC-2</u>

The aim of this project is to determine the role of the podoplanin-CLEC-2 signalling pathway during (1) embryonic development of vessels and organs, and (2) maintaining vascular integrity in adults during physiological processes including inflammation and wound healing.

The PI gave a presentation explaining the application to the Committee.

It is possible that the skin assay may be carried out at up to 3 sites on each animal, potentially reducing the number of animals required. This will be confirmed before the application is submitted.

It was noted that some of the required clarifications identified by the Committee in relation to the previous application (see minute 14/11-07-1) will also apply to this one (e.g. comments relating to the scoring used within BMSU, and the points at which animals will be humanely killed). In particular, it should be made explicit in the application that animals will not be left in pain – either analgesia will be adminstered or the animal will be humanely killed.

The Committee felt that the lay summary should be revisited to ensure that as far as possible, the focus is upon what will actually happen to the animals.

In the section on 'refinements', specific mention should be made to the good practices which are referenced elsewhere in the application, and also those activities which are seen as 'usual practice' within BMSU, but which still represent refinements.

The Committee discussed the use of tamoxifen pellets versus tamoxifen food. It was noted that podoplanin is very difficult to knock down in practice. In the past, tamoxifen injections have been used, but these have issues in terms of animal welfare and efficiency. Pellets are very simple to insert, and work over 3 weeks, systematically releasing enough tamoxifen to knock out the podoplanin. The pellets will be piloted before being used in the main experiments, and it is hoped that they will release the drug in a more uniform manner than is possible when using tamoxifen food.

In relation to terminal anaesthesia, it is essential that the animals remain completely unconscious throughout. Using the new downdraft table within BMSU allows CO_2 and isoflurane to be administered via the same mask, helping to ensure that the animals cannot regain consciousness.

After the PI left the meeting, the Committee continued its discussions. It was felt that the breeding numbers stated on the application are very low, but this is because the application reviewed previously (see minute 14/11-07-1) will supply animals for use in the current project licence. The breeding numbers stated in the current application relate specifically to podoplanin. The Committee considered how such 'shared' breeding could be best explained in the new-style licence application.

Resolved that:

With revisions as discussed above, the Chair will recommend that the Establishment Licence Holder submits the application to the Home Office.

14/11-08 Any Other Business

Request to supply mouse cadavers for applicant open days

BMSU has received a request to supply 70-100 mouse cadavers for dissection at applicant open days. It is proposed that applicants will be able to view testes and ovarian tissue under microscopes. There will be no additional animals used or welfare costs incurred.

Possible MEP visit

The Committee discussed the possibility of inviting an MEP to visit BMSU to help raise awareness of the importance of animal research, in light of recent calls within Europe to repeal the Directive on Animal Experimentation. Both BMSU and BERSC are happy to issue such an invitation.

14/11-09 Date of Next Meeting

The date of the next meeting is 15th January 2015.

GLOSSARY

3Rs	Replacement, Reduction and Refinement
BERSC	Biomedical Ethical Review Sub-Committee
BMedSci	Batchelor of Medical Science
BMSU	Biomedical Services Unit
CLEC-2	C-type lectin-like receptor 2
CO_2	Carbon Dioxide
GPVI	Glycoprotein VI (platelet)
LASA	Laboratory Animal Science Association
MEP	Member of European Parliament
MRI	Magnetic Resonance Imaging
NSAID	Non Steroidal Anti Inflammatory Drug
PI	Principal Investigator
RSPCA	Royal Society for the Prevention of Cruelty to Animals
TBA	To Be Announced